NTP Research Concept: *N*-Butylbenzenesulfonamide

Project Leader

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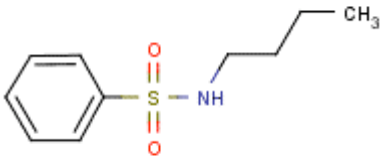
Background and Rationale



CAS No. 3622-84-2

N-Butylbenzenesulfonamide (NBBS) was nominated by the National Institute of Environmental Health Sciences to the National Toxicology Program (NTP) for comprehensive toxicological evaluation based on its extensive use and limited toxicity data. A complete toxicological literature review is available at http://ntp.niehs.nih.gov/go/165. NBBS is a common plasticizer used in polyacetals, polycarbonates, polysulfones, and polyamides (Nylon 11 and Nylon 12). It is a high production volume chemical with an aggregate U.S. production of 1 to <10 million lbs reported in 2006 [1]. NBBS has been detected in environmental samples including estuaries [2], runoff from agricultural fields [3, 4], and effluent from waste water treatment plants [5]. Additionally, most water treatment processes did not effectively remove NBBS [6], and NBBS was not found to be readily biodegradable [7]. Human exposure could occur from leaching of NBBS from polyamide cooking utensils (>10 μg/L) [8] or in an occupational setting [1]. Recently, NBBS was detected, but not quantified, in one out of 42 breast adipose tissue samples taken from 21 female patients in Spain [9].

Currently, there is insufficient toxicological data to adequately characterize potential human health risks of NBBS. Despite the limited toxicological data, there is evidence that NBBS targets multiple systems. Rapid uptake, distribution into tissues including brain, and elimination were observed in rats following intravenous administration of NBBS [10]. However, toxicokinetic studies have not been performed following oral administration of the chemical. Short-term oral administration of NBBS (50, 150, or 1000 mg/kg) resulted in hematological changes, central nervous system effects, and liver pathology in the middle and high dose groups [11]. Additional short-term studies in rats following either oral or inhalation exposure to NBBS indicated changes in hematopoietic cell counts [12]. Neurotoxicity, evidenced by motor dysfunction and pathological lesions in the brain, was observed in rabbits following administration of NBBS via intracisternal or intraperitoneal injection [13]. The observed *in vivo* neurotoxicity was further supported by *in vitro* cytotoxicity of NBBS to neuronal and glial

cells [14]. Adverse reproductive effects including histopathological lesions in the testis and epididymis were observed in male rats exposed to NBBS for 28 days via oral gavage [15]. Perinatal exposure of rats to NBBS resulted in developmental effects including pre- and post-implantation loss, postpartum pup loss, and generalized edema in pups [15]. However, perinatally-exposed rats were not evaluated at sexual maturity and the effects of *in utero* administration of NBBS on reproductive endpoints are unknown. Assessments of chronic toxicity, carcinogenicity, and immunotoxicity have not been performed with NBBS.

The cellular and molecular targets of NBBS leading to the observed reproductive and neurological toxicity remain obscure. NBBS was assessed in a high throughput screening battery as part of the EPA/NTP/NIH Chemical Genomics Center collaboration and was found to be relatively inactive (Tox21 High Throughput Screening Program, unpublished data). It did not interact with estrogen or androgen receptors, but did act as a weak agonist of RXR and weakly activated the cytochrome P450 enzyme CYP2C19 (Tox21 High Throughput Screening Program, unpublished data). Quantitative structure-activity relationship (QSAR) analyses performed using GeneGo models predicted neurological, carcinogenic, and genotoxic effects of NBBS, as well as anemia (see NBBS toxicological review document). The QSAR-predicted molecular targets that were identified by GeneGo (including cathepsins, neuropeptide receptor 5R, thromboxane A2 receptor, myosin light chain kinase, protein kinase C, and the γ-secretase complex) indicate that it could affect proteolysis and apoptosis, muscle contraction, platelet aggregation, and fetal development. Although QSAR-predicted targets and effects of NBBS require confirmation in bioassays, they appear to be compatible with available toxicity data.

Key Issues

Considering the limited amount of toxicological data and the clear indications of neurological and reproductive toxicity in animal models, comprehensive hazard characterization of NBBS is needed because there is a high likelihood of human exposure. Limited short-term exposure data and QSAR analyses strongly suggest that NBBS elicits hematological, neurological, reproductive, and developmental toxicity. QSAR models also predict carcinogenic effects; however, a carcinogenicity study has not been conducted with this compound. Additionally, an immunotoxicological assessment of NBBS has not been performed, despite indications that short-term exposure to this compound elicits changes in hematopoietic cell counts. The likely route of human exposure is oral, as NBBS has been detected in drinking water samples and has been found to leach from cooking utensils. Therefore, studies are needed following oral exposure to NBBS to characterize absorption, distribution, metabolism, and excretion of this environmental contaminant.

Specific Aims

- Characterize the dose-response effects of oral exposure to NBBS on target systems with a focus on hematological, neurological, reproductive, and developmental endpoints.
- Determine whether NBBS elicits immunotoxicity or carcinogenicity.

- Gather toxicokinetic and tissue data to estimate the doses of NBBS that correspond with observed toxicities in a rodent model.

Proposed Approach

Phase 1

In vitro – Assessment of potential endocrine activity and neurotoxicity assays
TK/ADME – rat and mouse, oral and intravenous exposure
In vivo toxicity

- Rat – perinatal oral exposure dose range finding study
- Mouse – adult oral exposure 14 day toxicity study

Phase 2

In vivo toxicity

- Rat – subchronic oral exposure including perinatal window to assess reproductive toxicity, teratogenicity, immunotoxicty, and neurotoxicity
- Mouse – adult oral exposure 90 day toxicity study

Phase 3

Carcinogenicity in both rat and mouse

Significance and Expected Outcome

Studies will address considerable data gaps for a high production volume chemical that is found in environmental samples and targets hematological, neurological, reproductive, and developmental endpoints. Dose-response data from these studies will inform the risk assessment of NBBS. Additionally, these studies will provide dosimetry data to create a bridge between measured environmental levels of NBBS to which humans might be exposed and observed toxicity in a rodent model. Information on NBBS will provide insight into the toxicological potential of related compounds that represent a relatively common and understudied group of industrial chemicals.

References

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